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# Hantavirus maintenance and transmission in reservoir host populations

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Hantaviruses are primarily hosted by mammalian species of the orders Rodentia, Eulipotyphla and Chiroptera. Spillover to humans is common, and understanding hantavirus maintenance and transmission in reservoir host populations is important for efforts to curtail human disease. Recent field research challenges traditional phases of virus shedding kinetics derived from laboratory rodent infection experiments. Organ infection sites in non-rodent hosts suggest similar transmission routes to rodents, but require direct assessment. Further advances have also been made in understanding virus persistence (and fadeouts) in fluctuating host populations, as well as occupational, recreational and environmental risk factors associated with spillover to humans. However, despite relevance for both intra-species and inter-species transmission, our understanding of the longevity of hantaviruses in natural environments remains limited.

## Addresses

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For a complete overview see the [Issue](#) and the [Editorial](#)

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## Introduction

Hantaviruses (family *Bunyaviridae*) are enveloped RNA viruses with a negative sense tri-segmented genome, encoding RNA-dependent RNA-polymerase, two surface glycoproteins, nucleocapsid protein N, and in some cases, a non-structural protein [1]. The latest taxonomical proposal lists 48 hantavirus species [2], which are present on every continent except Australia and Antarctica. These are hosted by mammalian species of the orders Rodentia,

Eulipotyphla and Chiroptera [3,4], with insect hosts also recently identified [5<sup>••</sup>].

Each hantavirus is associated with one or few closely related reservoir host species in which they cause mostly asymptomatic and persistent (probably life-long) infections. Although several host-switches — establishment in a secondary host species with onward transmission — have been described among wildlife species [6,7], it is a widely shared opinion that co-evolution (co-diversification) of hantaviruses with their respective reservoir hosts is the prevailing trend. Frequent spillover infections to humans, however, have established hantaviruses as an important group of zoonotic disease agents [8].

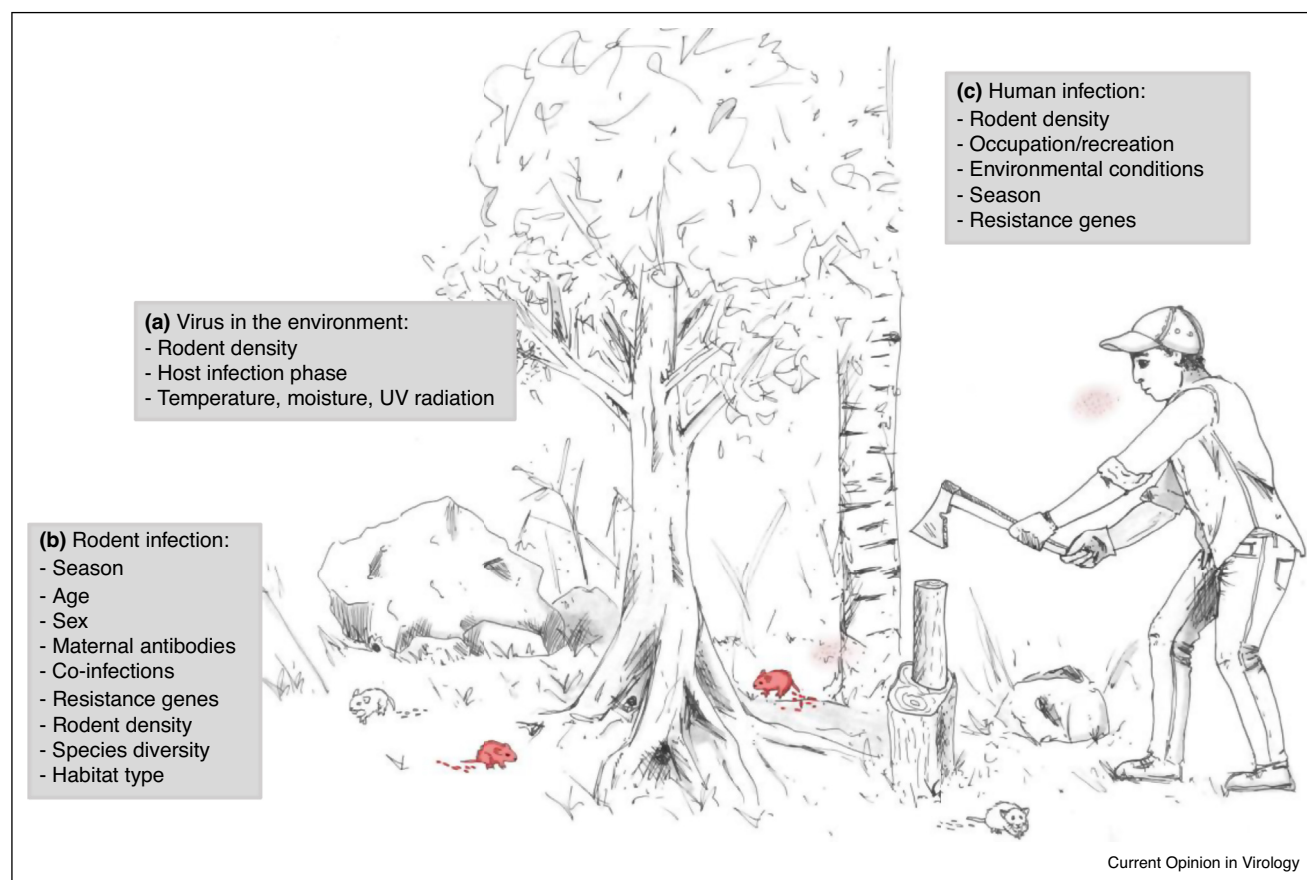
In order to devise strategies to mitigate and prevent human hantavirus infections, it is necessary to understand how these viruses are maintained and transmitted in their reservoir host species [9<sup>••</sup>]. Here we summarise current knowledge on this topic, and draw attention to recent advances and important gaps in understanding. Virus spillover to humans is also discussed, which is tightly linked to reservoir host population dynamics and is a consequence of mechanisms that facilitate intraspecies transmission.

## Mechanisms of transmission

The majority of knowledge pertaining to hantavirus transmission comes from a small number of well-studied rodent systems; particularly Puumala virus (PUUV) in bank voles (*Myodes glareolus*) and Sin Nombre virus (SNV) in deer mice (*Peromyscus maniculatus*). Most rodent hosts shed virus in their saliva, urine and faeces, with acquisition by conspecifics occurring via the inhalation of aerosolized virus in the environment (see [Figure 1](#)), and through intense contact, such as biting, grooming and sharing food resources (although these routes are usually difficult to demonstrate) [10–13,14<sup>••</sup>]. SNV and Andes virus (ANDV) are commonly shed in saliva, but conversely, have only rarely been identified in urine and faeces [15–17], suggesting that intense contact is primarily responsible for intraspecies transmission.

Across all systems, the relative importance of different transmission routes, including sex-biases and seasonal variation, remain outstanding questions. For example, aggressive encounters may be important for transmission during reproductive seasons, especially between males [13]. No direct evidence is available regarding virus shedding or transmission routes for shrew-borne, mole-borne

Figure 1



Synthetic depiction of a hantavirus transmission setting. A common route of transmission for many hantaviruses is the inhalation of aerosolized virus, which is shed into the environment in the saliva and excreta of infected rodents (depicted in red). Several factors are known or expected to influence the amount and persistence of infectious hantaviruses once outside the host **(a)**, and the risk of infection in conspecific rodents **(b)** and people **(c)**.

or bat-borne hantaviruses. However, the few studies to assess virus distribution in host tissues have identified similar patterns to rodents, suggesting comparable transmission routes; high viral loads in kidneys particularly support the notion of virus shedding in urine [18,19,20]. These assumptions nevertheless require direct validation. As habitat and behavioural characteristics of host species vary, especially across taxonomic orders, viruses are likely to experience some disparity in selection pressures acting on transmission.

Rodent viral loads and shedding in saliva and excreta peak approximately 2–4 weeks following initial infection, and then decrease over subsequent months despite the persistence of viral RNA in host tissues [12,13,21]. Consequently, hantavirus infections are often characterised by an initial acute infectious phase, followed by chronic infection with occasional or no virus shedding. However, this assumption is largely based on laboratory infection experiments, and is challenged by monitoring studies of naturally infected wild bank voles. These have found that

after an initial and comparable peak in shedding, a substantial proportion of voles continue to shed and transmit PUUV, probably throughout their lifetime [14,22]. Inherent differences between natural and laboratory settings may be responsible for these contrasting results. In the laboratory, for instance, hosts are usually provided with food *ad libitum*, whereas in the wild, finite energy resources may be traded-offs among immune defences and other pertinent processes, impairing the hosts' ability to control the infection [23].

### Virus persistence outside the host

Indirect inhalation is favoured as the dominant mode of intraspecies transmission for many hantaviruses due to the ease with which the virus can pass between rodents (for example between cages up to 1.5 m apart for PUUV [24]) and to people, and the longevity of infectious virus once shed into the environment (Figure 1). Clearly for viruses that are transmitted via indirect contact, the longevity of infectiousness once outside the host will

be selected for, and may also interact with other evolutionarily pliable traits such as virulence.

Live vole exposure experiments have demonstrated that PUUV remains infectious at room temperature for 12–15 days once outside the host [25]. Environmental conditions are expected to play an important role in the stability of hantaviruses, with cell culture experiments showing that cool and damp conditions are able to substantially prolong infectiousness [25,26]. Other environmental variables, such as UV radiation, are likely to have the opposite effect. However, the influence of environmental conditions on virus stability remains to be assessed in natural settings and with other hantavirus species.

### Heterogeneity in intraspecies transmission

Several factors are known to create individual-level heterogeneity in hantavirus infection risk. Maternal antibodies confer resistance to hantavirus infections in juvenile rodents for up to 80 days [15,22,27,28], while older individuals tend to be disproportionately infected, reflecting their accumulated exposure risk and the persistent nature of infections [13,29]. Male rodents also typically display higher infection prevalence than females [13,28,30], which may result from increased virus exposure due to both aggressive encounters and greater spatial movement. Research with bank voles suggests that resistance/tolerance genes and co-infections by other parasites can create additional heterogeneity in susceptibility [31–33]. Co-infections are particularly noteworthy, as their ability to influence infection dynamics in other host-parasite systems is increasingly recognised [34–36], but their effects on hantaviruses susceptibility and shedding dynamics have so far received little research attention.

The population-level effect of density-dependent transmission has been extensively studied, with mixed results [30]. This isn't surprising given that many studies rely on antibody detection to determine infection status, which usually fails to distinguish between new and old infections (but see [37]). Further confounding the identification of density-dependence is seasonal turnover in population age structure. Research with bank voles has shown that highest hantavirus prevalence typically occurs in early spring, when old, overwintered rodents predominate [29,38]. The introduction of susceptible juveniles through breeding during spring and summer then dilutes the proportion of infected individuals, despite a potential increase in the transmission rate [39].

Extending to a community level, hantavirus transmission is likely to decrease as species richness increases due to mechanisms which reduce contact between naïve and infected hosts or virus in the environment [40]. For example, high species diversity may reduce the abundance of reservoir hosts, or increase predator density, which encourages rodents to seek protective areas and

thereby restricts their movement and virus exposure opportunities. Evidence for this effect comes from studies with SNV in deer mice [41–43], and PUUV in bank voles [44,45]. However, the precise mechanism by which species diversity lowers infection prevalence is often not known (although density is sometimes accounted for).

Landscape effects on hantavirus transmission dynamics present an intriguing line of enquiry, with strong implications for spillover into humans (discussed below). Preliminary evidence suggests that transmission may be greatest in non-optimal host habitats, such as peri-domestic settings for deer mice and young forest stands for bank voles [13,46]; although patterns appear more complex at a micro-habitat scale [47]. Recent studies have examined the persistence of hantaviruses in fluctuating rodent populations, identifying regular fadeouts of PUUV, Dobrava-Belgrade virus (DOBV) and SNV [47,48,49]. Indeed, it was estimated that a sustained population density of at least 17 deer mice/ha is required for the invasion and persistence of SNV [48]. These studies highlight the meta-population structure in which hantaviruses exist, and emphasise the need for research to investigate mechanisms of connectivity that facilitate virus reintroduction to subpopulations (see for example [50]).

### Spillover infections

As hantaviruses are shed into the environment, exposure by non-reservoir host species is an invariable consequence. While spillover to sympatric rodents has been identified [51], human infection is by far the most extensively studied form of spillover. All currently known human hantaviruses infections are derived from rodents, with disease severity ranging from asymptomatic to fatal, and the case fatality rate and proportion of asymptomatic infections largely determined by the virus type and human genetic predispositions [52]. These infections are considered dead-end events for the virus, due to an absence of human-to-human transmission. One exception is known; Andes virus (ANDV), which can be occasionally transmitted among people [53]. While the details of how this occurs are not fully understood, ANDV seems to display unique anti-inflammatory properties and resist host salivary antiviral mechanisms [54,55].

Spatio-temporal variation in human infection risk is due to variation in exposure, reservoir host abundance, and virus stability (discussed above). People presumably become infected following inhalation of or direct contact with infectious virus present in wildlife host excreta and saliva. Certain occupations and activities increase the likelihood of virus exposure, including working in forestry and farming, and working with hay and fire wood, cleaning barns and forest cabins, and entering rodent infested buildings (Figure 1) [13,56,57]. As a result, agricultural practices and landscape changes play a significant role in determining the overall exposure risk [58,59]. Recently,

contact with pet rats has been identified as a source of Seoul hantavirus infections [60].

In northern Europe, where specialist predation is likely to regulate vole abundance [61], bank vole density is a reasonable proxy for human infection risk [62]. Meanwhile in temperate Europe, masting induced by warm summers is an important driver of hantavirus epidemics (mostly due to PUUV) [63]. A unique dataset from Central China covering half a century revealed that two climatic variables, temperature and rainfall, play key roles in reservoir host dynamics, and the rate of transmission and risk of Hantaan virus disease outbreaks [64]. Climate variables, in particular temperature, precipitation and rainfall, have similarly been highlighted as drivers of hantavirus cardiopulmonary syndrome outbreaks and nephropathia epidemica infections in other areas [58,65]. Climate not only affects reservoir host dynamics, but also human activities that increase exposure risk, such as seasonal agricultural activities [59] and time spent in the countryside [58,66].

## Conclusions

A key purpose of this review is to draw attention to recent developments pertaining to the maintenance and transmission of hantaviruses in their reservoir host populations. As outlined above, several advances have been made, which have in particular increased our understanding of shedding kinetics in wild rodent populations [14], heterogeneity in transmission dynamics [29,38], and occupational, recreational and environmental risk factors for human infection [57,59,64]. While the bank vole-Puumala virus system in northern Europe is by far the most extensively studied host-hantavirus relationship, recent studies on DOBV and SNV in fluctuating rodent populations have shed important light on the persistence and fadeouts of these hantaviruses in their reservoir host populations [48,49].

Despite these advances, significant knowledge gaps remain. Probably most glaring is that almost nothing is known regarding the transmission of hantaviruses in non-rodent hosts. Indeed, relatively little information is available for most rodent-borne hantaviruses. Future research is clearly required to address these deficiencies, and to also assess potential associations between lesser studied hantaviruses and human disease. Other notable areas for further research include seasonal variation in the relative importance of different transmission routes, the effects of environmental variables on virus longevity outside the host, the impact of concurrent infections by other parasites and pathogens on hantavirus susceptibility and shedding, and mechanisms of connectedness between meta-populations that facilitate virus reintroduction.

As the loss of natural habitats continues — due to factors such as land use changes and climate change — so too will

the movement of wildlife into urban and peri-urban environments [67]. Coupled with human occupations and recreations that encroach on natural wildlife habitat and increase the likelihood of exposure, hantavirus infections will remain a global threat to public health; including viruses currently known to science and potentially also those yet to be identified [68]. Understanding how hantaviruses are maintained and transmitted within populations of their reservoir hosts is critical to devising effective intervention strategies [9]. While recent advances have been made towards this endeavour, many important questions remain.

## Conflicts of interest

None.

## Acknowledgements

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